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A1
1. (Amended) A controlled-release glucosamine composition comprising a therapeutically effective amount of a glucosamine component dispersed in a controlled-release matrix system comprising a controlled-release component finely dispersed throughout said matrix system and capable of releasing said glucosamine in an amount and at a rate sufficient to maintain an effective glucosamine blood serum level over a designated time period, said controlled-release component comprising at least one water soluble high molecular weight cellulose polymer.

A2
15
~~16~~ 16. (Amended) A unit dosage for controlled delivery of glucosamine comprising a glucosamine component dispersed in a controlled-release matrix system comprising a controlled-release component finely dispersed throughout said matrix system and capable of providing a release profile which results in a substantially constant glucosamine release rate over a designated time period.

A3
17
~~18~~ 18. (Amended) The unit dosage of Claim ~~17~~¹⁶, wherein said controlled-release component is HPMC present in an amount of from about 8 to about 12 wt%, said HPMC having a molecular weight of about 85,000, and wherein said designated time period is about 12 hours.

18
~~19~~ 19. (Amended) A method for the treatment of conditions having an inflammatory component comprising:
administering to a human or animal having a condition with an inflammatory component a composition which contains a therapeutically effective amount of a glucosamine component dispersed in a controlled-release matrix system comprising a controlled-release component finely dispersed throughout said matrix system and capable of releasing said glucosamine in an amount and at a rate sufficient to maintain an effective glucosamine blood serum level over a designated time period, said controlled-release component comprising at least one water soluble high molecular weight cellulose polymer.

26
27. (Amended) A composition for the treatment of arthritis without adversely effecting glucose regulation, said composition comprising a therapeutically effective amount of a glucosamine component dispersed in a controlled-release matrix system comprising a controlled-release component finely dispersed throughout said matrix system and capable of releasing said glucosamine in an amount and at a rate sufficient to maintain an effective glucosamine blood serum level for treatment of arthritis, but not to exceed a glucosamine blood serum level which will affect an adverse change in glucose regulation, over a designated time period.

26
37. (Amended) A method for the treatment of arthritis without adversely effecting glucose regulation, said method comprising:
administering to a patient having arthritis a composition which comprises a therapeutically effective amount of a glucosamine component for the treatment of arthritis dispersed in a controlled-release matrix system comprising a controlled-release component finely dispersed throughout said matrix system and capable of releasing said glucosamine in an amount and at a rate sufficient to maintain an effective glucosamine blood serum level for the treatment of arthritis, but not to exceed a glucosamine blood serum level which will affect an adverse change in glucose regulation, over a designated time period.

REMARKS

Claims 1, 16, 18, 19, 27 and 37 have been amended and Claim 6 has been cancelled without prejudice. As such, Claims 1-5 and 7-48 are pending.

A. Amendments:

Claim 1 has been amended to clarify that the controlled-release component is finely dispersed throughout the matrix system and is capable of controlling the release rate of the glucosamine, and to recite that the controlled-release component includes at least one water

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soluble high molecular weight cellulose polymer. Support for amended Claim 1 can be found throughout the specification and more specifically at page 12, lines 11-19.

Claims 16, 18, 19, 27 and 37 have been amended to be consistent with Claim 1.

B. Rejections:

REJECTION OF CLAIMS 16-18

On page 3, section 7, of the Office Action, Examiner Jones rejected Claims 16-18 under 35 U.S.C. §103(a) as being unpatentable over Murch, et al. (U.S. Pat. No. 6,046,179).

The three criteria that must be met in order to establish a *prima facie* case of obviousness includes:

First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or combine reference teachings.

Second there must be a reasonable expectation of success.

Finally, the prior art reference (or references when combined) must teach or suggest all the claimed limitations. See MPEP §2142.

The teaching or suggestion to make the claimed combination (or modification) and the reasonable expectation of success must both be found in the prior art, and not based on applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).

The initial burden is on the examiner to provide some suggestion of the desirability of doing what the inventor has done. "To support the conclusion that the claimed invention is

directed to obvious subject matter, the reference must expressly or impliedly suggest the claimed invention or the examiner must present a convincing line of reasoning as to why the artisan would have found the claimed invention to have been obvious in light of the teachings of the references. *Ex parte Clapp*, 227 USPQ 972, 973 (Bd. Pat. App. & Inter. 1985).

The Murch et al. reference relates to a composition and method for treating inflammatory bowel disease (IBD). The method involves delivering N-acetylglucosamine to the bowel of a patient having IBD. The composition containing the N-acetylglucosamine can be delivered to the bowel directly in the form of a suppository or enema, or in the form of an orally ingestible time-release substance which can withstand degradation by the gastric acids of the stomach and can release the N-acetylglucosamine in the bowel or colon. (See Col. 2, lines 53-64).

The time-release composition includes an enteric coating which allows the N-acetylglucosamine to pass through the low pH portion of the digestive track, i.e. the stomach, and release in the higher pH range of intestinal fluids. The enteric coating is pH controlled and remains in tact until it reaches the intestinal fluids, where it then dissolves and releases the N-acetylglucosamine. (See col. 4, lines 21-43). There is no teaching or suggestion of a sustained release composition which provides a substantially constant release of the active ingredient over time.

In contrast, the presently claimed unit dosage (Claims 16-18) does not rely on an enteric coating. The unit dosage according to the invention includes a controlled-release matrix system, having the glucosamine material dispersed in it, in which the matrix system itself slowly dissolves and releases the glucosamine at a substantially constant rate.

Applicants respectfully submit that there is no teaching or suggestion by Murch et al. of the claimed matrix system which provides a substantially constant glucosamine release

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rate over a designed time period. Therefore, it is respectfully requested that the rejections of Claims 16-18 be withdrawn.

REJECTION OF CLAIMS 1-48

On page 3, section 8, of the Office Action, Examiner Jones rejected Claims 1-48 under 35 U.S.C. §103(a) as being unpatentable over Henderson et al. (U.S. Pat. No. 5,364,845), in view of Shell (U.S. Pat. No. 5,582,837), in further view of McClain et al.

The Henderson et al. reference is merely directed to a therapeutic composition which includes glucosamine and salts thereof, in combination with chondroitin sulfate and soluble salts of manganese. There is no teaching or suggestion of a controlled-release matrix system, which contain a controlled-release component as claimed.

The Shell reference is directed to sustained release oral drug dosage forms that include a tablet or capsule having a plurality of particles which contain the drug dispersed in an alkyl cellulose. Shell teaches that the tablet or capsule should be highly soluble so that the particles rapidly disperse in the stomach after the capsule is ingested. (See col. 5, lines 23-33).

In contrast, the compositions of the present invention do not include a plurality of particles, but instead rely on a continuous matrix having a controlled-release component finely dispersed throughout the matrix to provide a controlled release of the glucosamine component over a designated period of time.

As such, Shell actually teaches away from a composition that has a continuous matrix, as opposed to a combination of separate particles. Moreover, there is no teaching or suggestion in Shell for a controlled-release glucosamine composition.

Further, Shell clearly does not teach or even suggest using a water soluble high molecular weight cellulose polymer to control the release of the active ingredient (Claim 1); a controlled-release component consisting of a high molecular weight HPMC present in an amount from about 8 to about 12 wt %, based on the total weight of the composition (Claim 10); or a composition having a controlled release over a 12 hour period (Claims 14, 26, 45 and 48).

The McClain et al. reference is directed to the study of the hexosamine pathway and insulin resistance. McClain et al. teach that a side effect of excessive glucosamine administration can be an insulin resistance response. However, McClain et al. do not teach or even suggest methods or compositions for controlling the rate of glucosamine administration to avoid an insulin resistance response.

The prior art references must be considered as a whole and the examiner may not pick and choose from the various teachings within the references. The combination as a whole must render the claimed invention obvious in order to properly support an obviousness rejection.

Also, the cited prior art references must invite or suggest the combination in order to maintain the obviousness rejection. No such invitation or suggestion to combine the Henderson et al. reference with either of the Shell or McClain et al. references is present.

Accordingly, as none of the references taken separately or combined teach or suggest the presently claimed compositions or methods, it is respectfully requested that the rejections of Claims 1-48 be withdrawn.

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CONCLUSION

Accordingly, Applicants respectfully submit that the application as amended, including Claims 1-5 and 7-48, is now in proper form for allowance, which action is earnestly solicited. If resolution of any remaining issue is required prior to examination of the application, it is respectfully requested that the Examiner contact Applicants' undersigned attorney at the telephone number provided below.

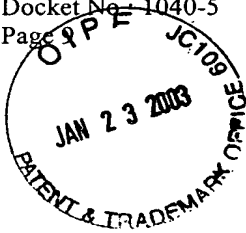
Respectfully submitted,



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VERSION OF AMENDMENT WITH MARKS
TO SHOW CHANGES MADE

IN THE CLAIMS:

Please cancel Claim 6 without prejudice.

Please amend Claims 1, 16, 18, 19, 27 and 37 as follows:

1. (Amended) A controlled-release glucosamine composition comprising a therapeutically effective amount of a glucosamine component dispersed in a controlled-release matrix system comprising a controlled-release component finely dispersed throughout said matrix system and capable of releasing said glucosamine in an amount and at a rate sufficient to maintain an effective glucosamine blood serum level over a designated time period, said [controlled-release matrix system comprising a] controlled-release component comprising [which comprises] at least one water soluble high molecular weight cellulose polymer.

16. (Amended) A unit dosage for controlled delivery of glucosamine comprising a glucosamine component dispersed in a controlled-release matrix system comprising a controlled-release component finely dispersed throughout said matrix system and capable of providing a release profile which results in a substantially constant glucosamine release rate over a designated time period.

18. (Amended) The unit dosage of Claim 17, wherein said [tablet comprises] controlled-release component is HPMC [is] present in an amount of from about 8 to about 12 wt%, said HPMC having a molecular weight of about 85,000, and wherein said designated time period is about 12 hours.

19. (Amended) A method for the treatment of conditions having an inflammatory component comprising:

administering to a human or animal having a condition with an inflammatory component a composition which contains a therapeutically effective amount of a glucosamine component dispersed in a controlled-release matrix system comprising a controlled-release component finely dispersed throughout said matrix system and capable of releasing said glucosamine in an amount and at a rate sufficient to maintain an effective glucosamine blood serum level over a designated time period, said [controlled-release system comprising a] controlled-release component [which comprises] comprising at least one water soluble high molecular weight cellulose polymer.

27. (Amended) A composition for the treatment of arthritis without adversely effecting glucose regulation, said composition comprising a therapeutically effective amount of a glucosamine component dispersed in a controlled-release matrix system comprising a controlled-release component finely dispersed throughout said matrix system and capable of releasing said glucosamine in an amount and at a rate sufficient to maintain an effective glucosamine blood serum level for treatment of arthritis, but not to exceed a glucosamine blood serum level which will affect an adverse change in glucose regulation, over a designated time period.

37. (Amended) A method for the treatment of arthritis without adversely effecting glucose regulation, said method comprising:

administering to a patient having arthritis a composition which comprises a therapeutically effective amount of a glucosamine component for the treatment of arthritis dispersed in a controlled-release matrix system comprising a controlled-release component finely dispersed throughout said matrix system and capable of releasing said glucosamine in an amount and at a rate sufficient to maintain an effective glucosamine blood serum level for the treatment of arthritis, but not to exceed a glucosamine blood serum level which will affect an adverse change in glucose regulation, over a designated time period.